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BP 897, a Selective Dopamine D_3 Receptor Ligand with Therapeutic Potential for the Treatment of Cocaine-Addiction

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ABSTRACT

BP 897 is a potent (K_i = 0.92 nM) dopamine D_3 receptor compound developed for the treatment of cocaine abuse and craving. BP 897 has a high selectivity for the dopamine D_3 versus D_2 receptors (70-fold) and a moderate affinity for 5-HT_{1A} receptors, (K_i = 84 nM), adrenergic-α_1 (K_i = 60 nM) and -α_2 adrenoceptors (K_i = 83 nM). BP 897 displays significant intrinsic activity at the human dopamine D_3 receptor by decreasing forskolin-stimulated cAMP levels and by stimulating mitogenesis of dopamine D_3-expressing NG108-15 cells. Although these findings suggest that BP 897 is a partial agonist, recent studies in Chinese Hamster Ovary (CHO) cells with expressed dopamine D_3 receptors demonstrated that BP 897 is devoid of any intrinsic activity but potently inhibits dopamine agonist effects (pIC_{50} = 9.43 and 9.51) in agonist-induced acidification rate or increase of GTPγS binding, respectively. In addition, BP 897 inhibits *in vivo* (EC_{50} = 1.1 mg/kg, i.v.) agonist-induced decrease of firing rate of dopaminergic neurons in the substantia nigra.

It has been clearly shown that BP 897, 1 mg/kg, i.p., reduces cocaine-seeking behavior in rats, without producing reinforcement on its own. In rhesus monkeys, BP 897 is not self-administered (up to 30 µg/kg, i.v.) but reduces cocaine self-administration. The potential usefulness of BP 897 in the treatment of drug-seeking behavior is further supported by its effects in drug conditioning models. Although BP 897 reduces L-DOPA–induced dyskinesia in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-treated monkeys, it provokes a return of parkinsonian symptoms. At high doses BP 897 has been reported to produce catalepsy in rats. Pharmacokinetic and toxicological data have not yet been published. These interesting preclinical findings with BP 897 provide additional validation for

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dopamine D_3 receptor as a therapeutic target for the treatment of cocaine abuse and its associated central nervous system (CNS) disorders. BP 897 recently entered phase II clinical studies.

INTRODUCTION

Cocaine Abuse and Related Disorders as a Therapeutic Indication

Cocaine, used in some South American traditional cultures to induce euphoria, has become one of the most abused psychostimulants in Western countries. It has been estimated that ca. 5.8 million people are regular users of cocaine in the United States (63). Cocaine is rapidly absorbed and distributed to all body tissues, producing important physiological and psychological effects (18,30,102). The main central nervous system (CNS)–mediated effects of cocaine include euphoria, agitation, anxiety, motor disturbances and psychotic episodes. Cocaine addiction is characterized by intermittent use, it is significantly reinforced by environmental cues, which may progress and escalate intake over time. Due to the development of tolerance and strong craving, repeated cocaine intake may lead to compulsive use and a state of physical dependency (20). In such cases, intake interruption leads to a severe withdrawal syndrome (18,21,102).

The effects of cocaine in animals parallel those in humans. Cocaine is self-administered by animals and its compulsive intake has fatal consequences. With unlimited access, death occurs after 2 weeks. Cocaine intake in animals, like in humans, is strongly modulated by environmental cues and cessation induces a withdrawal syndrome (38). Different animal models have been used to investigate putative new therapies for cocaine abuse and associated disorders, such as craving, withdrawal, and relapse (54). Abuse and dependence on cocaine, often complicated with abuse of other drugs, creates a dramatic medical and social burden for the individual (68). A significant percentage of the population in Western societies abuses or takes cocaine on a daily basis (102). Actually, 2.7% of cocaine users are addicted and around 17% of people taking cocaine have a risk of becoming addicted (63). Significant efforts have been made to find therapeutic agents to treat different phases of cocaine abuse behavior. Up-to-date, however, there is no successful therapy to either counteract the effects of cocaine or to treat concurrent psychological disorders (21,54). Therefore, antagonism of cocaine seeking behavior and of relapse after intake cessation remain the main objectives of current research in the field of cocaine addiction.

The Dopaminergic System and the Mechanisms of Cocaine Action in Brain

The brain areas directly involved in the actions of cocaine are also the anatomical targets of other psychostimulants. They include the ventral tegmental area (VTA), nucleus accumbens (NAC), frontal cortex (FCX), hippocampus (HIP), and amygdala (AMG). These areas are integrated in the so-called limbic system (36,102). Neurons in these regions express several receptors – nicotinic, opioid, serotonin and dopamine — known to be strongly involved in the modulation of mood and emotions. In particular, the reinforcing effects of cocaine involve the activity of neurons expressing dopamine D_2-like re-

ceptor subfamily in NAC, FCX, and VTA. The primary molecular effect of cocaine is the blockade of the dopamine transporter (22,78,80). Subsequently, both dopamine levels and dopamine receptor activity are altered. The progression of cocaine abuse involves different states; an important increase of dopaminergic activity is observed after cocaine ingestion, while a dopaminergic hypoactivity has been demonstrated after intake cessation (62,98). Although other neurotransmitter systems may also contribute to the effects of cocaine (76) the unequivocal role of the dopaminergic system supported the interest in the therapeutic potential of dopamine agonists and antagonists. Dopamine agonists have facilitated the understanding of cocaine reinforcing mechanisms and they might have potential utility in the treatment of some drug dependency disorders (26,54,68). However, the reinforcing effects of some dopamine agonists (2,89,97,101) preclude their clinical use because of their drug abuse liability. Dopamine D_1 receptor antagonism has also been considered, particularly because of its reduced side effect liability. However, the clinical interest of this therapeutic principle remains rather controversial (for review see ref. 54). In contrast, a dopamine D_1-like receptor agonist with potential anticraving effects is in phase II clinical evaluation (26,68). Several studies have demonstrated that the non-selective D_2 receptor antagonists, such as haloperidol or spiperone, may block the reinforcing effects of cocaine, but the net balance resulted in an increase rather than a reduction of cocaine intake (27,73,74). Dopamine D_2 receptor antagonists may help to treat cocaine-associated psychotic episodes (20,21), but extrapyramidal side effects (EPS) and hormonal actions associated with D_2 receptor blockade significantly reduce their therapeutic utility in the treatment of cocaine addiction. During the last decade, several studies suggested that partial agonists acting at dopaminergic D_2-like receptors might effectively treat cocaine seeking behavior (13,29,69,70). Actually, partial agonists are interesting pharmacological tools because their activity might be dependent on receptor occupancy by endogenous agonists. The use of dopamine D_2-like partial agonists may reduce increased dopaminergic activity after cocaine intake, but it may also maintain a low stimulation tonus after intake cessation. By maintaining a low level of receptor activation, these partial agonists may block cocaine-seeking behavior mechanisms associated with reduced dopamine stimulation (70). Pioneer studies suggested that partial agonism at D_3 receptors may have beneficial effects against cocaine abuse (13,69). However, these promising data raised many questions due to the somewhat low D_3/D_2 selectivity of the compounds used.

The Dopamine D_3 Receptor and the Treatment of Cocaine Craving

Recently, the use of more selective dopamine receptor ligands furthered our understanding of the role of dopamine receptors in cocaine craving and withdrawal syndromes. Numerous studies have implicated dopamine D_3 receptors in the mechanisms of psychostimulant addiction (2,13,14,43,52,59,85,95). The dopamine D_3 receptor was cloned and sequenced early in the 1990s (86). It is a seven-transmembrane domain receptor with sequence homology to the D_2-like receptor subfamily, which also includes the D_2 and D_4 receptors (87, 88). The D_3 receptor is a G-protein-coupled receptor and its stimulation leads to a reduction of intracellular cAMP levels by inhibiting adenylate cyclase, apparently through $G\alpha_{\alpha o}$ and $G_{\alpha i}$ G-proteins (82,86–88,94). Dopamine D_3 receptor expression has been demonstrated in different regions of the human and rodent brain by using *in situ* hybridization and northern blots. Particularly high levels of D_3 receptor mRNA transcripts have been detected in olfactory bulb, hypothalamus, islands of Calleja (ICJ), FCX, VTA,

and cerebellum (39,40,58,86,87,88). Radioligand binding studies using D_3-selective compounds have confirmed the presence of D_3 receptor protein in these areas (39,40,45,48, 58,88,90). Although all of the physiological functions of D_3 receptors have not been determined, their anatomical distribution in the limbic system suggests a role in controlling mood and emotional states (31,39,58,86). The affinity of typical and atypical antipsychotics strongly support this D_2-like receptor as an interesting therapeutic target for treatment of neuropsychiatric disorders such as schizophrenia, psychosis, and Parkinson's disease (32,47,86,87,88).

Data obtained in studies combining neuroanatomical techniques with the assessment of functional parameters (or by using knockout mice) have shown the presence of functional D_3 receptors in the mesolimbic dopaminergic system (1,19,35,37,49,72,104). This brain system is the anatomical substrate of the reinforcing actions of several drugs of abuse and brain reward mechanisms (36,101). In a seminal article, Caine and Koob (13) reported that R(+)7-OH-DPAT, a D_3-selective compound, was able to reduce cocaine self-administration at doses that do not induce reinforcement. A recent study using a paradigm of cocaine self-administration in rhesus monkeys demonstrated that dopamine antagonists decreased response rates and cocaine intake in a dose-dependent manner, with their rank order potency correlating to their dopamine D_3 receptor affinity (59). It has also been shown that D_3 selective agonists, such as PD 128907 or R(+)7-OH-DPAT, could replace cocaine as a discriminative stimulus in rats (2) and monkeys (85). R(+)7-OH-DPAT promoted reinstatement of lever press responding in an animal model of drug seeking behavior, indicating that D_3 agonism may induce relapse after cocaine cessation (84). Cocaine abuse may induce molecular changes, such as receptor expression or activation of immediate early genes, possibly affecting the brain reward system and leading, in turn, to tolerance, compulsive use, and the psychological changes observed during withdrawal (24,41,77,91,93,94,96). In contrast to previous observations on dopamine D_1 and D_2 receptors (53), an increase of dopamine D_3 receptor binding has been observed in the mesolimbic brain areas (caudate, putamen, NAC, and SN) of human subjects who died from cocaine abuse (90). Similarly, post-mortem analysis of human brains after cocaine-induced death revealed that NAC displays increased levels of dopamine D_3 mRNA transcripts (83). Taken together, these data demonstrate that dopamine D_3 receptors are involved in cocaine-reinforcing effects and strongly support the hypothesis that this receptor is an important target for treatment of cocaine abuse and seeking-behavior. Recent studies performed with the dopamine D_3 receptor selective compounds BP 897 and SB 277011A represent a significant progress in this direction (7,66,95; see below).

CHEMISTRY, ORIGIN, AND PROPRIETARY POSITION

BP 897 or BP 4.897 (N-4-[4-(2-methoxyphenyl)-1-piperazinyl]butylnaphtalene-2-carboxamide), previously known as DO 897, is a 2-naphthamide derivative of arylpiperazines (Fig. 1). BP 897 originated in the drug discovery program of Bioproject, an academic-industry joint venture based in France. BP 897 and several other analogues were synthesized by a CNRS/Bioproject group and disclosed in the European patent application (EP00779284) as compounds with agonist activity at D_3 receptors useful in the treatment of Parkinson's disease or as compounds with partial agonist activity useful in the treatment of drug addiction, withdrawal, depression, and psychotic disorders. During

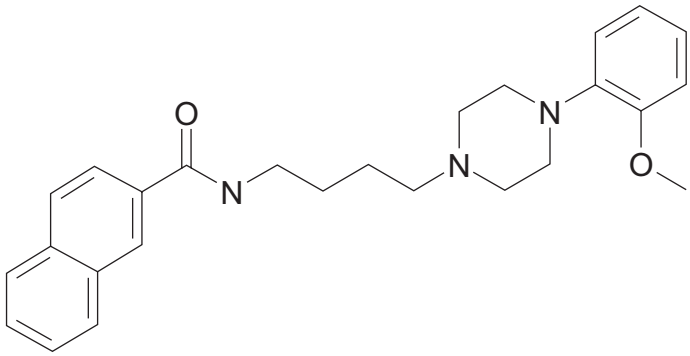

Fig. 1. Chemical structure of BP-897, N-{4-[4-(2-methoxyphenyl)-1-piperazinyl]butyl}naphtalene-2-carboxamide.

the last 2 years, two groups at INSERM (France) and Cambridge University (UK) investigated BP 897 for its potential use in the treatment of cocaine-seeking behavior. BP 897 entered phase I studies in 1999 in the United Kingdom as well as in France, but its development has been discontinued in the United Kingdom (Table 1). BP 897 is currently in a phase II study in France for the treatment of cocaine, nicotine and alcohol addiction, schizophrenia, and Parkinson's disease (81).

IN VITRO PHARMACOLOGY OF BP 897

Receptor Binding Profile

BP-897 binds with high affinity (K_i = 0.92 nM) to dopamine D_3 receptors expressed in CHO cells (66; Table 2). BP 897 is 70-fold more selective for human dopamine D_3 versus human dopamine D_2 receptors, as shown by its lower affinity (K_i = 61 nM) at hD_2 receptors expressed in both CHO and COS-7 cells (66,79,103). Some investigators found a somewhat lower binding affinity to D_3 receptors using CHO cells, but the D_3/D_2 selec-

TABLE 1. BP897 development history, status, therapeutic indications and licensing opportunities

Year	Status	Coverage	Therapeutic Indication	Licensing
1995	Patent EP0779284A1	Europe	Drug addiction, withdrawal, depression, psychotic disorders	
1998	Preclinical	England		
		France	Cocaine withdrawal	
1999	Phase I Clinical Trial	France England	Cocaine abuse and withdrawal	
2001	Developemt Discontinued	England		
	Phase II Clinical Trial	France	Cocaine addiction, nicotine addiction, alcohol addiction, schizophrenia, Parkinson's disease	EU, USA, Asia, Middle East, South America

tivity ratio was similar to that reported earlier (103). BP 897 displays very low affinity to dopamine D_1 and D_4 receptors (66; Table 2). The activity and the affinity of BP 897 at other G-protein-coupled receptors have not been extensively studied. However, it has been shown that BP 897 displays moderate to high affinity to 5-HT_{1A}, as well as α_1- and α_2-adrenoceptors (K_i = 84, 60, and 83 nM, respectively). BP 897 has very low or negligible affinity at 5-HT_7, muscarinic, histamine, or opiate receptors (66).

Functional Activity at D_3 Receptors

Although the pharmacological effect of BP 897 has been unequivocally shown in several animal models of dopaminergic activity (see below), the *in vitro* intrinsic activity of BP 897 remains controversial (Table 3). In early studies, it was reported that BP 897 activated adenylate cyclase and mitogenesis in NG108-15 cells expressing human dopamine D_3 receptors. BP 897 potently inhibited (EC_{50} = 1 nM) forskolin-induced cAMP synthesis (66) and increased (EC_{50} = 3 nM) [^{3}H]thymidine incorporation (64,66). The intrinsic activity of BP 897 was clearly lower (E_{max} = 55%) than that reported for full agonists (E_{max} = 100%), such as dopamine and quinpirole, suggesting that BP 897 may act *in vitro* as a partial agonist at human D_3 receptors (Table 3).

Recent studies have investigated the activity of BP 897 using different functional assays in CHO cells permanently expressing human dopamine D_3 receptors (100,103). It has been previously demonstrated that stimulation of human D_3 receptors induces changes in acidification rates (15). Wood et al (103) have clearly shown that BP 897 did not induce any change of acidification rate, while the D_2/D_3 agonists, quinpirole and BHT 920, dose-dependently induced a maximal response, in agreement with their full agonism *in vivo* (17). BP 897 potently inhibited the acidification rate response of quinpirole in a competitive manner (pK_b = 9.43). These findings are in agreement with its binding affinity at human dopamine D_3 receptors and demonstrate its antagonist properties; however, they are in contrast to previous data (64,66). Discrepancies between the pharmacology of a given receptor expressed in different heterologous cell systems may be due to receptor reserve, promiscuity of intracellular signals, G-protein/receptor imbalance or efficacy in functional coupling (60). It is difficult to explain the discrepancy observed for BP 897 between CHO and NG108-15 cells by different levels of receptor reserve or functional cou-

TABLE 2. Binding affinity (pK_i) of BP897 at different human dopamine receptors expressed in cell lines

Receptor	pK_i	Cell lines	Radioligand	Reference
hD_3	9.03	CHO cells	[^{125}I]iodosulpiride	66
hD_3	9.38	COS-7 cells	[^{3}H]nemonapride	79
hD_3	8.80	CHO cells	[^{125}I]iodosulpiride	103
hD_2	7.21	CHO cells	[^{125}I]iodosulpiride	66
hD_2	7.22	CHO cells	[^{125}I]iodosulpiride	103
hD_2	7.61	COS-7 cells	[^{3}H]nemonapride	79
hD_4	6.52	CHO cells	[^{125}I]iodospiperonene	66
hD_1	5.52	CHO cells	[^{3}H]SCH23390	66
hD_5	6	Not reported	Not reported	66

pling. Actually, BP 897 induced a mitogenic response in D_3/NG108-15 cells close to BHT 920 (E_{max} = 68% versus 55%) (66). Data provided by Wood et al (103) demonstrated the presence of significant receptor reserve in D_3/CHO cells. In such a system, even a weak partial agonist would have a strong agonistic activity, as with BHT 920, and this activity was not detected for BP 897 (103). Induction of mitogenesis is an endpoint located well downstream from receptor signaling cascades and can only be measured after long incubation periods. Therefore, promiscuity between different intracellular signals cannot be ruled out in this assay.

Because of the known reinforcing effects of dopamine agonists (2,85,89,97,101), it is very important to precisely define the intrinsic activity of a new therapeutic agent developed to treat cocaine addiction. In order to investigate the intrinsic activity of BP 897, we have studied its effect at human D_3 receptor/G-protein coupling, a functional mechanism occurring directly after ligand-receptor interaction (100). In this assay, quinpirole, dopamine, and the D_3 selective compound PD 128907 possessed a strong intrinsic activity suggesting full agonism; this is in agreement with other studies (51,61,94). BP 897 was unable to modify the basal levels of [^{35}S]GTPγS, while it dose-dependently inhibited the effect of dopamine (pIC_{50} = 9.51). These values correlate with the reported (66) affinity at hD_3 receptor (K_d = 0.92 nM). The lack of intrinsic activity, as well as the antagonism observed in both microphysiometer and GTPγS binding assays, strongly suggest that BP 897 is an antagonist at the human dopamine D_3 receptor.

IN VIVO CNS PHARMACOLOGY

BP 897-Induced Modulation of c-fos Expression in Brain

It has been shown that neuroleptics induce the expression of c-fos, an immediate early gene, in rat brain (16,50,75). This activity is associated with antagonism at dopamine D_2-like receptor family and agonism at dopamine D_1 receptors (66,72). The anatomical pattern of induced c-fos expression by dopaminergic antagonists correlates with the locali-

TABLE 3. Functional activity of BP897 at human dopamine D_2 and D_3 receptors expressed in different cell lines

Receptor	pEC_{50}	Intrinsic activity	Cell line	Functional Assay	Assay effect	Reference
hD_3	8.52	Partial agonist (55%)	NG108-15	Mitogenesis	[^{3}H]Thymidine incorporation	64,66
hD_3	9.00	Partial agonist (59%)	NG108-15	Adenylate cyclase	Forkolin-induced cAMP	66
hD_3	9.43[a]	Antagonist	CHO	Microphysiometry	Acidification rate	103
hD_3	9.51[b]	Antagonist	CHO	G-protein coupling	Agonist-induced GTPγS binding	100
hD_2	7.29[a]	Antagonist	CHO	Mitogenesis	[^{3}H]Thymidine incorporation	66
hD_2	8.05[a]	Antagonist	CHO	Microphysiometry	Acidification rate	103

Note. [a] pK_b values; [b] pIC_{50}.

zation of D_2 and D_3 receptors (55). Interestingly, D_3 receptor selective antagonists are able to induce c-fos expression in the Islands of Cajella, a major site of D_3 receptor expression (25,72). Pilla et al (66) have clearly shown that BP 897 dose-dependently (0.3–3 mg/kg, i.p.) induced the expression of c-fos in rat brain (Table 4). Moreover, BP 897 (1 mg/kg, i.p.) was able to potentiate the expression of c-fos triggered by D_1-receptor selective agonist SKF 39393 (10 mg/kg, i.p.) in rats, an effect related to antagonism at dopamine D_2/D_3 receptors (33,72). BP 897-induced potentiation of SKF 39393 effect on c-fos expression was observed also in wild-type mice but not in dopamine D_3 receptor-knockout mice (66), suggesting a direct role of dopamine D_3 receptors in this response (Table 4). Interestingly, BP 897 alone minimally induced c-fos expression in control mice, which contrasts observations in rats (66). Whether these differences are due to a BP 897, species-specific activity remains to be elucidated.

TABLE 4. Pharmacological effects of BP 897 in animals

Receptor	ED_{50}/activity i.p.	Dose, mg/kg i.p.	Species	Area	Comments	Reference
D_2 receptor occupancy	15 mg/kg	—	Mouse	Striatum	[^{3}H]N-PNAP[a]	66
D_3 receptor occupancy	0.5 mg/kg	—	Mouse	Striatum	[^{3}H]N-PNAP[a]	66
Catalepsy	12 mg/kg	—	Rat			66
SKF3893 induced contralateral rotation in 6-OHDA treated rats	Potentiate	1	Rat		After L-DOPA Sensitization	43 66
Stereotypy	Inactive	—	Mouse			66
Firing rate (SN)	Inactive	8	Rat	Substantia nigra		100
Quinpirole-inhibited firing rate	1.1 mg/kg	—	Rat	Substantia nigra		100
Hypothermia	Inactive	5	Rat			64
R(+)7-OH-DPAT-induced hypothermia	Inactive/ Active	5 >5	Rat			64
c-fos induction	0.3 mg/kg		Rat	Islands of Calleja		66
	Inactive?		Mouse	Islands of Calleja		66
c-fos induction by SKF38393	Potentiate	1	Rat	Islands of Calleja		66
	Potentiate	1	Mouse	Islands of Calleja		66
	Inactive	1	D_3-KO Mouse	Islands of Calleja		66
c-fos induction by cocaine-associated cues	Reduce			Somatosensory cortex		42
c-fos induction by morphine conditioning	Reduce		Mouse	Somatosensory cortex	Place preference	42

[a] [^{3}H]N-propylnorapomorphine.

Electrophysiological Effects of BP 897 in the Dopaminergic System

The inhibition of the firing rate of dopaminergic neurons in the nigrostriatal system is a characteristic of D_3-selective agonists, while antagonists are devoid of any inhibitory effect in this electrophysiological assay (37,44,65,99). Dopamine D_3 receptor selective agonists, such as PD 128907 and 7-OH-DPAT, potently inhibit the firing rate of dopaminergic neurons from VTA and substantia nigra (SN) (10,11,44,57,100). It has been shown that agonist-induced inhibition in this model correlates with the affinity to dopamine D_3, but not to D_2 receptors (37). Our *in vitro* data using the GTPγS binding assay (Table 3) suggest that BP 897 is an antagonist at human D_3 receptors expressed in heterologous cell systems (100). In the same publication we described that BP 897 has a similar pharmacological activity in dopaminergic neurons *in vivo* (100). At doses up to 8 mg/kg, i.v., BP 897 had no effect on spontaneous activity of SN neurons (Table 4). In addition, BP 897 dose-dependently reversed the effect of D_3/D_2 agonist quinpirole (100), strongly suggesting *in vivo* dopaminergic antagonism. These findings are in agreement with the reported inhibitory effects of other dopaminergic antagonists, such as haloperidol, clozapine, L 741626, or the D_3 receptor-selective compound S 33084 (10,11,34,56) in the agonist-induced inhibition of neuronal firing. The ED_{50} of BP 897 (1.1 mg/kg, i.v.) was in full agreement with its reported efficacy on D_3 receptor-modulated c-fos expression (Table 4) and dopamine D_3 receptor-mediated L-DOPA sensitization (43,66). Moreover, the ED_{50} of BP 897 for inhibiting agonist-induced decrease of dopaminergic firing rate is identical to its ED_{50} in cocaine-seeking behavior model in rats (66). Therefore, BP 897 acts *in vivo* as a dopamine D_3 antagonist when it inhibits agonist-induced decrease of firing rate of SN neurons. This activity is in agreement with the reported *in vitro* potency and intrinsic activity of BP 897 (100,103).

Effects of BP 897 in Animal Models of Cocaine Abuse and Drug Seeking Behavior

Several studies have demonstrated the important role of dopamine D_3 receptor in the effects of cocaine and psychostimulants (2,13,14,59,83,90; see also Table 5). The potential of partial agonism at D_3 receptors as a therapeutic principle is supported by the effects of BP 897 in animal models of cocaine abuse. BP 897 on its own, did not show any reinforcing effect in rats (66), while pretreatment with BP 897 in a rat model for drug seeking behavior potently and dose-dependently reduced responding (66). Although this effect was reported to be blocked by the D_3 selective compound, nafadotride (66), it may not be mediated by D_3 receptors. The authors did not report the blocking dose of nafadotride, and it has been reported that nafadotride occupies dopamine D_2 receptors at relatively low doses (ca. 1 mg/kg, s.c., or 3 mg/kg, i.p.) (46). In the rat model for cocaine craving, cocaine administered during the drug seeking period induced an increase in response which was not modified by BP 897 (66). Additional data in support of the anti-craving properties of BP 897 have been recently reported in models of conditioned activity (4,12,42). BP 897 (1 mg/kg, i.p.) blocked amphetamine conditioned activity when administered in the post-conditioning period, but did not modify either amphetamine conditioning per se or normal activity (4; Table 5). BP 897 blocked cocaine-conditioned hyperactivity in rats similarly to SB 277011-A, a D_3 selective antagonist (42). In the same study, BP 897 was reported to block also nicotine conditioned activity and morphine-in-

TABLE 5. Efficacy of BP 897 in animal models for drug abuse and drug seeking behavior

Receptor	Activity	Dose	Species	Area	Comments	Reference
Self-administration	Inactive	0.05 mg/i.v. infusion	Rats			66
	Inactive	3–30 μg/kg, i.v	Rhesus monkeys			7
Cocaine self- administration	Inactive	Up to 1 mg/kg, i.p	Rat		Continuous reinforcing	66
	Active	10 mg/kg, i.p	Mice		schedule	7
	Active	–	Monkey			6,7
Cocaine seeking behavior	Reduced	1 mg/kg, i.p	Rat		Second order schedule	66
Amphetamine conditioning	Inhibited	1 mg/kg, i.p	Rat		Paired stimuli	4
Cocaine conditioning	Inhibited				Paired stimuli	42
Nicotine conditioning	Inhibited				Paired stimuli	42
Morphine place preference	Inhibited				Paired stimuli	42
Cocaine conditioning	Inhibited		Rat	N. Accumbens (shell)	10 mg/kg cocaine daily Parameter electrical activity	12
Heroin seeking behavior	Inactive		Rat			67
Heroin reinforcing effects	Inactive		Rat			67

duced place preference (42). In a different rat model of drug conditioned responses, BP 897 blocked not only the behavioral activity associated with cocaine administration cued by visual signals, but also reduced electrical signals between the VTA and NAC (12). BP 897 was ineffective in a model of heroin seeking behavior in rats (67). All these data together, strongly suggest that BP 897 is an antiseeking behavior compound with a broad spectrum of therapeutic application. Whether this activity is due to weak partial agonism or antagonism at dopamine D_3 receptors remains to be elucidated (4,42). Data obtained in mice further support the potential for BP 897 in the treatment of psychostimulant abuse and associated disorders. BP 897 was able to reduce cocaine and D-amphetamine discriminative stimulus in mice (7). However, the dose used in this study (10 mg/kg, i.p.) strongly suggests that the effect of BP 897 could be due not only to dopamine D_3 but also D_2 receptor occupation.

The effects of BP 897 have also been studied in rhesus monkeys. At doses up to 30 µg/kg, i.v., BP-897 did not display reinforcing effects (7). The authors mentioned that at the doses used BP-897 may have been behaviorally active because of overt signs of sedation. However, no data on plasma levels of the compound have been reported, making it difficult to rule out that plasma levels of BP 897 were insufficient to induce reinforcing. It will be important to determine whether BP 897 at higher doses (>30 µg/kg, i.v.) may have reinforcing effects. It has also been reported that BP 897 is able to reduce cocaine self-administration in rhesus monkeys (6). Altogether, these data demonstrate that BP 897 is active in blocking cocaine craving behavior but not the reinforcing effect liability.

Catalepsy

Catalepsy is a central mechanism induced by typical neuroleptics and is clearly associated with antagonism at D_2 receptors in nigrostriatal pathways. Catalepsy represents an indicator of putative liability for parkinson-like EPS. BP 897 induced catalepsy (ED_{50} = 12 mg/kg, i.p.) in rats (66); this effect correlated with its affinity (K_i = 61 nM) and the maximal occupancy (ED_{50} = 15 mg/kg, i.p.) at dopamine D_2 receptors (66; Table 4). These results clearly show that, at higher doses, BP 897 binds to dopamine D_2 receptors *in vivo*.

Hypothermia

Some authors reported a correlation between dopamine agonist induced hypothermia and binding affinity to dopamine D_3 receptors, suggesting a participation of these receptors in the control of body temperature (3,56). In contrast, studies conducted in dopamine D_3 and D_2 receptor knockout mice suggest that D_2, rather than D_3 receptors, are implicated in the mechanism of thermoregulation (8,9,64). BP 897 at doses below 5 mg/kg, i.p., was unable to either affect body temperature or to reverse the hypothermic effect of R(+)7-OH-DPAT (66; Table 4). The lack of activity of BP 897 on body temperature might be interpreted differently. The compound may be an antagonist at D_3 receptors, as suggested by some *in vitro* data (100,103); or dopamine D_3 receptor agonism may not be involved in thermoregulation, as some studies in knockout mice indicated (8,9,64).

At higher doses (>5 mg/kg, i.p.) BP 897 potentiated the hypothermic effect of a s.c. injection of 160 µmol/kg (s.c.) R(+)7-OH-DPAT. At this dose BP 897 should block not only

dopamine D_3 but also D_2 receptors. The reason for lack of efficacy of BP 897 in reversing D_2 agonist mediated hypothermia (64) remains, therefore, unclear. An additive effect of BP 897 with R(+)7-OH-DPAT suggests that either BP-897 or a putative metabolite are active at a pharmacological target involved in body temperature control. It remains to be elucidated, however, whether it is through an action at dopamine D_2 or D_3 receptors. It has been demonstrated that 5-HT_{1A} agonism induces a reduction of body temperature (5). Due to the moderate to high affinity of BP 897 (K_i = 84 nM) for this serotoninergic receptor (66), an action on the 5-HT_{1A} receptor cannot be excluded, and may explain the observed potentiation effect.

PHARMACOKINETICS, METABOLISM, SAFETY, AND SIDE EFFECTS

Although detailed information on the metabolism or pharmacokinetics of BP 897 is missing, some important indications can be inferred from the data published to date. Studies performed in rodents and monkeys demonstrate that BP 897 is a CNS active compound via multiple routes of administration — i.v., s.c., and i.p. Results obtained using BP 897 as a radioligand further demonstrated a good brain bioavailability (28). Studies regarding stability, pharmacokinetics, metabolism, and bioavailability have been announced, but currently no information is available in the public domain. Efficacious plasma levels are unknown; however, a very low dose (0.5 mg/kg, i.p.) BP 897 is active in cocaine-seeking behavior model, suggesting a high potency. Furthermore, BP 897 (1 mg/kg, i.p.) induces an increase in c-fos expression in rat brain (Table 4). However, this effect appears to be minimal in mice (66). Whether this is due to a species-specific metabolism, pharmacokinetic, or brain bioavailability remains unknown.

Toxicological data and the side-effect profile of BP 897 have not been reported so far; thus, the therapeutic window for efficacy versus side effects remains unknown. It should be stressed that BP 897 induced catalepsy (ED_{50} = 12 mg/kg, i.p.) in rats (66) and also induced a return of parkinsonian symptoms in MPTP-treated monkeys previously treated with L-DOPA (92). Thus, the compound has EPS liability, likely due to its dopamine D_2 receptor affinity. Moreover, BP 897 potentiates R(+)7-OH-DPAT hypothermic effect (64) indicating an interaction, at higher doses (>5 mg/kg, i.p.), with an additional receptor, possibly 5-HT_{1A}.

BP 897 clearly produced sedative effects in monkeys. However, whether these effects are due to BP 897 action at D_3 or other receptors remains unclear. Although no data are available on the intrinsic activity of BP 897 at adrenergic α_1 and serotonin 5-HT_{1A} receptors, the reported affinity might suggest blood pressure changes as a putative side effect associated with increasing doses. In monkeys, high doses (>30 μg/kg, i.v.) of BP 897 may induce ptosis and lethargy (7). Altogether, these data suggest that the therapeutic window for BP 897 will need to be carefully monitored.

Metabolic and pharmacokinetic data are not available in the public domain. A phase I study for BP 897 was initiated in 1999, but to our knowledge, no data have been reported. Due to this important void of information, it is rather difficult to fully assess the therapeutic potential of BP 897 as a candidate for the treatment of cocaine seeking behavior.

POTENTIAL OF BP 897 FOR THE TREATMENT OF COCAINE ADDICTION, WITHDRAWAL, AND OTHER NEUROPSYCHIATRIC DISORDERS

BP 897 is one of the most selective dopamine D_3 receptor compounds disclosed so far. The potential of BP 897 for the treatment of cocaine abuse and associated disorders, in particular cocaine craving and relapse after withdrawal, is strongly supported by results obtained in rodents and primates (6,7,66; Table 5). The efficacy of BP 897 in animal models for drug conditioning using other psychostimulants suggests it has a broad potential for the treatment of drug-seeking behavior (Table 5) The claimed partial agonism of BP 897 may ensure the necessary stimulation of dopamine D_3 receptors in the mesolimbic system to avoid relapse. However, discordant data (66,100,103) on intrinsic activity of BP 897 *in vitro*, complex interpretation of *in vivo* D_3 selective activity, as well as the missing pharmacokinetic information, do not allow for a conclusive validation of the therapeutic principle — partial agonism at dopamine D_3 receptor — for the treatment of cocaine abuse and craving. Actually, a very recent study shows that SB 277011-A, a selective dopamine D_3 receptor antagonist, blocked not only cocaine-seeking behavior (6 mg/kg, i.p.) but also cocaine-induced place preference (1–10 mg/kg, i.p.) and electrical brain stimulation reward (3 mg/kg, i.p.) (95). These findings are somewhat opposed to the theory of dopamine D_3 partial agonism as effective treatment of cocaine addiction, and they suggest that BP 897 effects are due to dopamine D_3 receptor antagonism. The availability of additional dopamine D_3 receptor compounds with increased selectivity may significantly help in future investigations of this promising therapeutic approach. A recent structure-activity relationship study disclosed some BP 897 derivatives with better selectivity ratios (23). The exciting results with BP 897 warrant additional therapeutic validation studies.

Recently, there has been increasing interest in the dopamine D_3 receptor as a target for the treatment of Parkinsons's disease and associated disorders (32). However, the reported effects of BP 897 in MPTP-treated monkeys as well as its D_2/D_3 antagonism are likely to exclude any use of this compound in Parkinson's disease. The seminal papers reporting the cloning and expression of the dopamine D_3 receptors emphasized the putative importance of this D_2-like receptor for the treatment of psychosis and schizophrenia (25,31,32, 86). During the last decade, significant data have been accumulated supporting this hypothesis (71). Several companies have disclosed the development of dopamine D_3 receptor antagonists for the treatment of psychosis (25). Taking into account the reported partial agonism (66) or even antagonism (100,103) of BP-897, it is worth considering this compound, like other D_3 receptor antagonists, as a good candidate to treat schizophrenia and psychosis, including those induced by cocaine. The selectivity of BP 897 for D_3 versus D_2 receptors, the reported D_3 antagonism, and its excellent brain penetration support BP 897 as a good candidate to be an atypical neuroleptic. Interestingly, current phase II studies included schizophrenia and psychotic disorders as therapeutic indications. No studies addressing this hypothesis in animal models have been published yet, but they will probably appear in the future.

APPENDIX

Chemical Names

BHT 920, 6-allyl-5,6,7,8-tetrahydro-4H-thiazolo[4,5-d]azepin-2-amine;

7-OH-DPAT, 7-hydroxy-dipropylaminotetralin hydrobromide

L 741626, 3-[4-(4-chlorophenyl-4-hydroxypiperidino)methyl]indole

MPTP, N-methyl-4-phenyl-1,2,3,6-tetrahydropyridine

Nafadotride, N[(n-butyl-2-pyrrolidinyl)methyl]-1-methoxy-4-cyano naphtalene-2-carboxamide

PD 128907, (+)-trans-3,4,4a,10b-tetrahydro-4-propyl-2H,5H-[1]benzopyrano[4,3b]-1,4-oxazin-9-ol

Quinpirole, (4aR-trans)-4,4a, 5,6,7,8,8a,9-octahydro-propyl-1H-pyrazolo[3,4-g]quinoline

S 33084, (3aR,9bS)-N-[4-(8-cyano-1, 3a,4,9b-tetrahydro-3H-benzopyrano[3,4-c]pyrrole-2-yl)-butyl]-(4-phenyl) benzamide

SB 277011-A, trans-N-[4-[2-(6-cyano-1,2,3,4-tetrahydroisoquinolin-2-yl)ethyl]cyclohexyl]-4-quinolininecarboxamide

SKF 38393, 1-phenyl-2,3,4,5-tetrahydro-(1H)-3-benzazepine-7,8-diol

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REFERENCES

1. Accili D, Fishburn CS, Drago J, et al. A targeted mutation of the D_3 dopamine receptor gene is associated with hyperactivity in mice. *Proc Natl Acad Sci USA* 1996;93:1945–1949.
2. Acri JB, Carter SR, Alling K, et al. Assessment of cocaine-like discriminative stimulus effects of dopamine D_3 receptor ligands. *Eur J Pharmacol* 1995;281:R7–R9.
3. Audinot V, Newman-Tancredi A, Gobert A, et al. A comparative *in vitro* and *in vivo* pharmacological characterization of the novel dopamine D_3 receptor antagonists (+)-S 14297, nafadotride, GR 103,691 and U 99194. *J Pharmacol Exp Ther* 1998;287:187–197.
4. Aujla H, Sokoloff P, Beninger RJ. A dopamine D_3 receptor partial agonist blocks the expression of conditioned activity. *Neuroreport* 2002;13:173–176.
5. Aulakh CS, Wozniak KM, Haas M, Hill JL, Zohar J, Murphy DL. Food intake, neuroendocrine and temperature effects of 8-OHDPAT in the rat. *Eur J Pharmacol* 1988;146:253–259.
6. Beardsley PM. Is there a role for dopamine D_3R agents in drug abuse? *Behav Pharmacol Soc Eur Behav Pharmacol Soc* 1999;[Abstract].
7. Beardsley PM, Sokoloff P, Balster RL, Schwartz JC. The D_3R partial agonist, BP 897, attenuates the discriminative stimulus effects of cocaine and D-amphetamine and is not self-administered. *Behav Pharmacol* 2001;12:1–11.
8. Boulay D, Depoortere R, Rostene W, Perrault G, Sanger DJ. Dopamine D_3 receptor agonists produce similar decreases in body temperature and locomotor activity in D_3 knock-out and wild-type mice. *Neuropharmacology* 1999;38:555–565.
9. Boulay D, Depoortere R, Perrault G, Borrelli E, Sanger DJ. Dopamine D_2 receptor knock-out mice are insensitive to the hypolocomotor and hypothermic effects of dopamine D_2/D_3 receptor agonists. *Neuropharmacology* 1999;38:1389–1396.
10. Bowery B, Rothwell LA, Seabrook GR. Comparison between the pharmacology of dopamine receptors mediating the inhibition of cell firing in rat brain slices through the substantia nigra pars compacta and ventral tegmental area. *Br J Pharmacol* 1994;112:873–880.
11. Bowery BJ, Razzaque Z, Emms F, et al. Antagonism of the effects of (+)-PD 128907 on midbrain dopamine neurones in rat brain slices by a selective D_2 receptor antagonist L-741,626. *Br J Pharmacol* 1996;119: 1491–1497.
12. Bressand K, Louvel J, Sokoloff P. Role of D_3 dopamine receptor in cocaine-cue conditioning: An *in vivo* electrophysiological study. *Dopamine* 2002;P2.4:126 [Abstract].

13. Caine SB, Koob GF. Modulation of cocaine self-administration in the rat through D_3 dopamine receptors. *Science* 1993;260:1814–1816.
14. Caine SB, Koob GF, Parsons LH, Everitt BJ, Schwartz JC, Sokoloff P. D_3 receptor test *in vitro* predicts decreased cocaine self-administration in rats. *Neuroreport* 1997;8:2373–2377.
15. Coldwell MC, Boyfield I, Brown AM, Stemp G, Middlemiss DN. Pharmacological characterization of extracellular acidification rate responses in human D_2 (long), D_3 and $D_{4.4}$ receptors expressed in Chinese hamster ovary cells. *Br J Pharmacol* 1999;127:1135–1144.
16. Deutch A, Lee MC, Iadarola M. Regionally specific effects of atypical antipsychotic drugs on striatal Fos expression: The nucleus accumbens shell as a locus of antipsychotic action. *Mol Cell Neurosci* 1992;3: 332–341.
17. Eriksson E, Svensson K, Clark D. The putative dopamine autoreceptor agonist B-HT 920 decreases nigral dopamine cell firing rate and prolactin release in rat. *Life Sci* 1985;36:1819–1827.
18. Fischman MW, Johanson CE. Cocaine. In: Schuster Ch. R., Kuhar MJ, Eds. *Pharmacological aspects of drug dependence*. Vol. 118. Heidelberg: Springer-Verlag, 1996:159–195.
19. Frantz K, Babcock D, Van Hartesveldt C. The locomotor effects of a putative dopamine D_3 receptor agonist in developing rats. *Eur J Pharmacol* 1996;302:1–6.
20. Gawing FH. Neuroleptic reduction of cocaine-induced paranoia but not euphoria. *Psychopharmacology (Berl)* 1986;90:142–143.
21. Gawing FH. Cocaine addiction: Psychology and neurophysiology. *Science* 1991;251:1580–1586.
22. Giros B, Jaber M, Jones SR, Wightman RM, Caron MG. Hyperlocomotion and indifference to cocaine and amphetamine in mice lacking the dopamine transporter. *Nature* 1996;379:606–612.
23. Gmeiner P, Hübner H, Bettinetti L, Schlotter K. Highly selective dopamine D_3 receptor partial agonists: Molecular design and pharmacological investigations. *Dopamine* 2002;P1.24:74 [Abstract].
24. Graybiel AM, Moratalla R, Robertson HA. Amphetamine and cocaine induce drug-specific activation of the c-fos gene in striosome-matrix compartments and limbic subdivisions of the striatum. *Proc Natl Acad Sci USA* 1990;87:6912–6916.
25. Gross G, Bialojan S, Drescher K, et al. Evaluation of D_3 receptor antagonists. *Eur Neuropsychopharmacol* 1997;7:S120.
26. Haney M, Collins ED, Ward AS, Foltin RW, Fischman MW. Effect of a selective dopamine D_1 agonist (ABT-431) on smoked cocaine self-administration in humans. *Psychopharmacologia* 1999;143:102–110.
27. Herrling S, Woods JH. Chlorpromazine effects on cocaine-reinforced responding in rhesus monkeys: Reciprocal modification of rate-altering effects of drugs. *J Pharmacol Exp Ther* 1980;214:354–361.
28. Huang Y, Martinez D, Simpson N, Guo N, Montoya J, Laruelle M. Synthesis and evaluation of [C-11] BP 897 as a potential PET radioligand for Da D_3 receptor. *Soc Neurosci* 2000;[Abstract].
29. Hubner CB, Koob GF. Bromocriptine produces decreases in cocaine self-administration in the rat. *Neuropharmacology* 1990;3:101–108.
30. Jaffe JH. Drug addiction and drug abuse. In: Goodman Gilman A, Rall TW, Nies AS, et al., Eds. *The pharmacological basis of therapeutics.* New York: McGraw-Hill Inc., 1992:522–573.
31. Joyce JN. Dopamine D_3 receptors, from anatomy to neuropsychiatry. *NeuroSci News* 1999;2:11–21.
32. Joyce JN. Dopamine D_3 receptor as a therapeutic target for antipsychotic and antiparkinsonian drugs. *Pharmacol Ther* 2001;90:231–259.
33. Jung MY, Schmauss C. Decreased c-fos responses to dopamine D_1 receptor agonist stimulation in mice deficient for D_3 receptors. *J Biol Chem* 1999;274:29406–29412.
34. Kelland MD, Freeman AS, Chiodo LA. (+/–)-3,4-Methylenedioxymethamphetamine-induced changes in the basal activity and pharmacological responsiveness of nigrostriatal dopamine neurons. *Eur J Pharmacol* 1989;169:11–21.
35. Koeltzow TE, Xu M, Cooper DC, et al. Alterations in dopamine release but not dopamine autoreceptor function in dopamine D_3 receptor mutant mice. *J Neurosci* 1998;18:2231–2238.
36. Koob GF. Drugs of abuse: Anatomy, pharmacology and function of reward pathways. *TIPS* 1992;13: 177–184.
37. Kreiss DS, Bergstrom DA, Gonzalez AM, Huang KX, Sibley DR, Walters JR. Dopamine receptor agonist potencies for inhibition of cell firing correlate with dopamine D_3 receptor binding affinities. *Eur J Pharmacol* 1995;277:209–214.
38. Kuhar MJ, Pilotte NS. Neurochemical changes in cocaine withdrawal. *TIPS* 1996;17:260–264.
39. Landwehrmeyer B, Mengod G, Palacios JM. Dopamine D_3 receptor mRNA and binding sites in human brain. *Brain Res Mol Brain Res* 1993;18:187–192.
40. Landwehrmeyer B, Mengod G, Palacios JM. Differential visualization of dopamine D_2 and D_3 receptor sites in rat brain. A comparative study using *in situ* hybridization histochemistry and ligand binding autoradiography. *Eur J Neurosci* 1993;5:145–153.

41. Laurier LG, Corrigall WA, George SR. Dopamine receptor density, sensitivity and mRNA levels are altered following self-administration of cocaine in the rat. *Brain Res* 1994;634:31–40.
42. Le Foll B, Frances H, Ferry S, Diaz J, Schwartz JC, Sokoloff P. The dopamine D_3 receptor modulates reactivity to cocaine, morphine, and nicotine-associated cues: Role of the somatosensory cortex. *Dopamine* 2002;P2.10:132 [Abstract].
43. Le Foll B, Schwartz JC, Sokoloff P. Dopamine D_3 receptor agents as potential new medications for drug addiction. *Eur Psychiatry* 2000;15:140–146.
44. Lejeune F, Millan MJ. Activation of dopamine D_3 autoreceptors inhibits firing of ventral tegmental dopaminergic neurones *in vivo*. *Eur J Pharmacol* 1995;275:R7–R9.
45. Levant B, Grigoriadis DE, DeSouza EB. [3H]quinpirole binding to putative D_2 and D_3 dopamine receptors in rat brain and pituitary gland: A quantitative autoradiographic study. *J Pharmacol Exp Ther* 1993;264: 991–1001.
46. Levant B, Vansell NR. *In vivo* occupancy of D_2 dopamine receptors by nafadotride. *Neuropsychopharmacology* 1997;17:67–71.
47. Levant B, Ling ZD, Carvey PM. Dopamine D_3 receptors. Relevance for the drug treatment of Parkinson's disease. *CNS Drugs* 1999;12:391–402.
48. Levesque D, Diaz J, Pilon C, et al. Identification, characterization, and localization of the dopamine D_3 receptor in rat brain using 7-[^{3}H]hydroxy-N,N-di-n-propyl-2-aminotetralin. *Proc Natl Acad Sci USA* 1992;89: 8155–8159.
49. Lin JY, Yen SH, Shieh KR, Liang SL, Pan JT. Dopamine and 7-OH-DPAT may act on D_3 receptors to inhibit tuberoinfundibular dopaminergic neurons. *Brain Res Bull* 2000;52:567–572.
50. MacGibbon GA, Lawlor PA, Bravo R, Dragunow M. Clozapine and haloperidol produce a differential pattern of immediate early gene expression in rat caudate-putamen, nucleus accumbens, lateral septum and islands of Calleja. *Brain Res Mol Brain Res* 1994;23:21–32.
51. Malmberg A, Mikaels A, Mohell N. Agonist and inverse agonist activity at the dopamine D_3 receptor measured by guanosine 5′-gamma-thio-triphosphate-^{35}S-binding. *J Pharmacol Exp Ther* 1998;285:119–126.
52. Mash DC. Are neuroadaptations in D_3 dopamine receptors linked to the development of cocaine dependence? *Mol Psychiatry* 1997;2:7–8.
53. Meador-Woodruff JH, Little KY, Damask SP, Mansour A, Watson SJ. Effects of cocaine on dopamine receptor gene expression: A study in the postmortem human brain. *Biol Psychiatry* 1993;34:348–355.
54. Mello NK, Negus SS. Preclinical evaluation of pharmacotherapies for treatment of cocaine and opioid abuse using drug self-administration procedures. *Neuropsychopharmacology* 1996;14:375–424.
55. Merchant KM, Figur LM, Evans DL. Induction of c-fos mRNA in rat medial prefrontal cortex by antipsychotic drugs: Role of dopamine D_2 and D_3 receptors. *Cerebral Cortex* 1991;6:561–570.
56. Millan MJ, Peglion JL, Vian J, et al. Functional correlates of dopamine D_3 receptor activation in the rat *in vivo* and their modulation by the selective antagonist, (+)-S 14297. 1. Activation of postsynaptic D_3 receptors mediates hypothermia, whereas blockade of D_2 receptors elicits prolactin secretion and catalepsy. *J Pharmacol Exp Ther* 1995;275:885–898.
57. Millan MJ, Gobert A, Newman-Tancredi A, et al. S33084, a novel, potent, selective, and competitive antagonist at dopamine D_3-receptors. I. Receptorial, electrophysiological and neurochemical profile compared with GR218,231 and L741,626. *J Pharmacol Exp Ther* 2000;293:1048–1062.
58. Murray AM, Ryoo HL, Gurevich E, Joyce JN. Localization of dopamine D_3 receptors to mesolimbic and D_2 receptors to mesostriatal regions of human forebrain. *Proc Natl Acad Sci USA* 1994;91:11271–11275.
59. Nader MA, Green KL, Luedtke RR, Mach RH. The effects of benzamide analogues on cocaine self-administration in rhesus monkeys. *Psychopharmacologia* 1999;147:143–152.
60. Newman-Tancredi A, Conte C, Chaput C, Verriele L, Millan MJ. Agonist and inverse agonist efficacy at human recombinant serotonin 5-HT_{1A} receptors as a function of receptor: G-protein stoichiometry. *Neuropharmacology* 1997;36:451–459.
61. Newman-Tancredi A, Cussac D, Audinot V, Pasteau V, Gavaudan S, Millan MJ. G-protein activation by human dopamine D_3 receptors in high-expressing Chinese hamster ovary cells: A guanosine-5′-O-(3-[^{35}S]thio)-triphosphate binding and antibody study. *Mol Pharmacol* 1999;55:564–574.
62. Ng JP, Hubert GW, Justice JB Jr. Increased stimulated release and uptake of dopamine in nucleus accumbens after repeated cocaine administration as measured by *in vivo* voltammetry. *J Neurochem* 1991;56: 1485–1492.
63. O'Brien CP. Drug addiction and drug abuse. In: Hardman JG, Limbird LE, Eds. *The pharmacological basis of therapeutics*. 10th Edition. McGraw-Hill, 2001:621–642.
64. Perachon S, Betancur C, Pilon C, Rostene W, Schwartz JC, Sokoloff P. Role of dopamine D_3 receptors in thermoregulation: A reappraisal. *Neuroreport* 2000;11:221–225.

65. Piercey MF, Hoffmann WE, Smith MW, Hyslop DK. Inhibition of dopamine neuron firing by pramipexole, a dopamine D_3 receptor-preferring agonist: Comparison to other dopamine receptor agonists. *Eur J Pharmacol* 1996;312:35–44.
66. Pilla M, Perachon S, Sautel F, et al. Selective inhibition of cocaine-seeking behaviour by a partial dopamine D_3 receptor agonist. *Nature* 1999;400:371–375.
67. Pilla M, Hutcheson DM, Adib-Samil P, Potton E, Everitt BJ. Seeking responses for cocaine, heroin and natural reinforcers are differentially modulated by dopamine D_3 receptors. *Soc Neurosci* 2001;27:647.16
68. Pouletty P. Drug addictions: Towards socially accepted and medically treatable diseases. *Nat Rev Drug Discovery* 2002;1:731–736.
69. Pulvirenti L, Koob GF. Lisuride reduces intravenous cocaine self-administration in rats. *Pharmacol Biochem Behav* 1994;47:819–822.
70. Pulvirenti L, Koob GF. Dopamine receptor agonists, partial agonists and psychostimulant addiction. *TIPS* 1994;15:374–379.
71. Richtand NM, Woods SC, Berger SP, Strakowski SM. D_3 dopamine receptor, behavioral sensitization, and psychosis. *Neurosci Biobehav Rev* 2001;25:427–443.
72. Ridray S, Griffon N, Mignon V, et al. Coexpression of dopamine D_1 and D_3 receptors in islands of Calleja and shell of nucleus accumbens of the rat: Opposite and synergistic functional interactions. *Eur J Neurosci* 1998;10:1676–1686.
73. Roberts DCS, Vickers G. Atypical neuroleptics increase self-administration of cocaine: An evaluation of a behavioural screen for antipsychotic activity. *Psychopharmacology (Berl)* 1984;82:135–139.
74. Roberts DCS, Loh EA, Vickers G. Self-administraton of cocaine on a progressive ratio schedule in rats: Dose-response relationship and effect of haloperidol pretreatment. *Psychopharmacology (Berl)* 1989;97: 535–538.
75. Robertson GS, Fibiger HC. Neuroleptics increase c-fos expression in the forebrain: Contrasting effects of haloperidol and clozapine. *Neuroscience* 1992;46:315–328.
76. Rocha B. Cocaine self-administration in dopamine-transporter knockout mice. *Nat Neurosci* 1998;1: 132–137.
77. Ruskin DN, Marshall JF. Amphetamine- and cocaine-induced fos in the rat striatum depends on D_2 dopamine receptor activation. *Synapse* 1994;18:233–240.
78. Scanley BE, Gandelman MS, Laruelle M, et al. [^{123}I]IPCIT and [^{123}I][beta]-CIT as SPECT tracers for the dopamine transporter: A comparative analysis in nonhuman primates. *Nucl Med Biol* 2000;27:13–21.
79. Scarselli M, Novi F, Schallmach E, et al. D_2/D_3 dopamine receptor heterodimers exhibit unique functional properties. *J Biol Chem* 2001;276:30308–30314.
80. Schoemaker H, Pimoule C, Arbilla S, Scatton B, Javoy-Agid F, Langer SZ. Sodium-dependent [^{3}H]cocaine binding associated with dopamine uptake sites in the rat striatum and human putamen decrease after dopamine denervation and in Parkinson's disease. *Naunyn-Schmiedeberg's Arch Pharmacol* 1985;329:227–235.
81. SCRIP. Bioproject acquires GlaxoSmithKline research unit. *SCRIP World Pharm News* 2001;2679:11.
82. Seabrook GR, Kemp JA, Freedman SB, Patel S, Sinclair HA, McAllister G. Functional expression of human D_3 dopamine receptors in differentiated neuroblastoma × glioma NG108-15 cells. *Br J Pharmacol* 1994;111: 391–393.
83. Segal DM, Moraes CT, Mash DC. Up-regulation of D_3 dopamine receptor mRNA in the nucleus accumbens of human cocaine fatalities. *Brain Res Mol Brain Res* 1997;45:335–339.
84. Self DW, Barnhart WJ, Lehman DA, Nestler EJ. Opposite modulation of cocaine-seeking behavior by D_1- and D_2-like dopamine receptor agonists. *Science* 1996;271:1586–1589.
85. Sinnott RS, Mach RH, Nader MA. Dopamine D_2/D_3 receptors modulate cocaine's reinforcing and discriminative stimulus effects in rhesus monkeys. *Drug Alcohol Depend* 1999;54:97–110.
86. Sokoloff P, Giros B, Martres MP, Bouthenet ML, Schwartz JC. Molecular cloning and characterization of a novel dopamine receptor D_3 as a target for neuroleptics. *Nature* 1990;347:146–151.
87. Sokoloff P, Giros B, Martres MP, et al. Localization and function of the D_3 dopamine receptor. *Arzneimittelforschung* 1992;42:224–230.
88. Sokoloff P, Martres MP, Giros B, Bouthenet ML, Schwartz JC. The third dopamine receptor D_3 as a novel target for antipsychotics. *Biochem Pharmacol* 1992;43:659–666.
89. Spealman RD, Bergman J, Madras BK, Kamien JB, Melia KF. Role of D_1 and D_2 dopamine receptors in the behavioral effects of cocaine. *Neurochem Int* 1992;20(Suppl):147S–152S.
90. Staley JK, Mash DC. Adaptive increase in D_3 dopamine receptors in the brain reward circuits of human cocaine fatalities. *J Neurosci* 1996;16:6100–6106.
91. Steiner H, Gerfen CR. Cocaine-induced c-fos messenger RNA is inversely related to dynorphin expression in striatum. *J Neurosci* 1993;13:5066–5081.

92. Tahar H, Grondin R, Doan VD, et al. Behavioural effects of selective dopamine D_3 receptor agonist/antagonist in primate model of Parkinson's disease. *Soc Neurosci* Abstr 1999;25:640.
93. Unterwald EM, Ho A, Rubenfeld JM, Kreek MJ. Time course of the development of behavioral sensitization and dopamine receptor up-regulation during binge cocaine administration. *J Pharmacol Exp Ther* 1994;270:1387–1396.
94. Vanhauwe JF, Fraeyman N, Francken BJ, Luyten WH, Leysen JE. Comparison of the ligand binding and signaling properties of human dopamine D_2 and D_3 receptors in Chinese hamster ovary cells. *J Pharmacol Exp Ther* 1999;290:908–916.
95. Vorel SR, Ashby CR Jr, Paul M, et al. Dopamine D_3 receptor antagonism inhibits cocaine-seeking and cocaine-enhanced brain reward in rats. *J Neurosci* 2002;22:9595–9603.
96. Wallace DR, Mactutus CF, Booze RM. Repeated intravenous cocaine administration: Locomotor activity and dopamine D_2 /D_3 receptors. *Synapse* 1996;23:152–163.
97. Wedd MR, Vanover KE, Woolverton WL. Reinforcing effect of the D_1 agonist SKF 81297 in rhesus monkeys. *Psychopharmacology (Berl)* 1993;113:51–52.
98. Weiss F, Markou A, Lorang MT, Koob GF. Basal extracellular dopamine levels in the nucleus accumbens are decreased during cocaine withdrawal after unlimited-access self-administration. *Brain Res* 1992;593: 314–318.
99. Werkman TR, Kruse CG, Nievelstein H, Long SK, Wadman WJ. *In vitro* modulation of the firing rate of dopamine neurons in the rat substantia nigra pars compacta and the ventral tegmental area by antipsychotic drugs. *Neuropharmacology* 2001;40:927–936.
100. Wicke K, Garcia-Ladona J. The dopamine D_3 receptor partial agonist, BP 897, is an antagonist at human dopamine D_3 receptors and at rat somatodendritic dopamine D_3 receptors. *Eur J Pharmacol* 2001;424: 85–90.
101. Wise RA. Neurobiology of addiction. *Curr Opin Neurobiol* 2000;6:243–251.
102. Withers NW, Pulvirenti L, Koob GF, Gillin JC. Cocaine abuse and dependence. *J Clin Psychopharmacol* 1995;15:63–78.
103. Wood MD, Boyfield I, Nash DJ, Jewitt FR, Avenell KY, Riley GJ. Evidence for antagonist activity of the dopamine D_3 receptor partial agonist, BP 897, at human dopamine D_3 receptor. *Eur J Pharmacol* 2000;407: 47–51.
104. Zapata A, Witkin JM, Shippenberg TS. Selective D_3 receptor agonist effects of (+)-PD 128907 on dialysate dopamine at low doses. *Neuropharmacology* 2001;41:351–359.